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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,688	12/20/2001	Osamu Asano	0425-0867P	7785

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER

PATEL, SUDHAKER B

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 06/27/2003

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/018,688

Applicant(s)

ASANO ET AL.

Examiner

Sudhaker B. Patel, D.Sc.Tech.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) 14,15,22,24,26-33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13,20,21,23,25 and 34-36 is/are rejected.
- 7) ☒ Claim(s) 16-19 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2,6,7,8.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) (in part) 1-13,16-21,13,25,34-36, drawn to compounds, compositions, a method of use and the first recited process of making Formula (I) wherein both W and Q are N i.e. purine ring. If this group is elected further restriction will be required as there are many variable e.g. R1-R3 and AR with multiples of meanings.

Group II, claim(s) (in part) 1-12,15,16-19,21,23-25,34-36, drawn to compounds, compositions, a method of use and the first recited process of making Formula (I) wherein one of W and Q is N and the other is carbon i.e. pyrido-imidazole ring. If this group is elected further restriction will be required as there are many variable e.g. R1-R3 and AR with multiples of meanings.

Group III, claim(s) (in Part) 1, 14,15,22,24,26-33, drawn to compounds not included in above Groups I, II, and other processes of making the same e.g. when both Q & W are carbons forming Ben-imidazole ring, intermediate(s) e.g. claim 22, and processes not included in inventions I & II. . If this group is elected further restriction will be required as there are many variable e.g. R1-R3 and AR with multiples of meaning

2. The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The compounds, and their method of use do not represent a single inventive concept which is common to all groups. The compounds represent different structures.

3. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

- (1). Purine which is a heterocycle with 6:5 bicyclic ring combination with 4 N, and has variables R1-R3, Ar.
- (2). Pyrido-imidazole which is a heterocycle with 6:5- bicyclic ring combination with 3N, and has variables R1-R3, Ar.
- (3). Benzo-imidazole which is a heterocycle with 6:5-bicyclic ring combination with 2 N, and has variables R1-R3, Ar.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The following claim(s) are generic: 1-11,16-19,20,21,23-36.

4. The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or

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corresponding special technical features for the reasons that they are different chemical structures which are not art recognized equivalents.

5. During a telephone conversation with Mr. M. Weiner on 4/22/02 a provisional election was made without traverse to prosecute the invention of Group I, claims(in part) 1-13,16-21,13,25,34-36. Affirmation of this election must be made by applicant in replying to this Office action.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Applicants have elected invention of Group I and species of Example 46 as recited on page 108 of specification (= 5-[6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone). Since claims 1-13,16-21,13,25,34-36 link with other inventions, this application will be examined bearing in mind the subject matter related to elected invention of Group I and species of Example 46 only.

7. Search was carried out with species for the Formula (I) with variables defined as follows:

Ar	= 3-Fluoropheny;
R1	= NH ₂ ;
R2	= H;
R3	= N-Mehtyl-2-pyridone;
W	= N ;
Q	= N.

Applicants are reminded of the election of species guidelines provided in MPEP 803.02, which are followed for examination.

The elected species was not found. Therefore, search was expanded to:

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Ar = Optionally substituted aryl;
R1 = H, Halogen, alkyl, -N(alkyl)2;
R2 = H, Halogen, alkyl;
R3 = Optionally substituted aryl, alkyl ;
W = N ;
Q = N,

Variables as defined above, and art(s) were found.

As per the guide lines outlined earlier, the search was limited to W, Q = both them N; Ar= optionally substituted phenyl, and the variables:

R1 = -N(C1-8Alkyl)2, -NH2, H, halogen, alkyl;
R2 = H, Halogen, alkyl;
R3 = - N-Mehtyl-2-pyridone, Optionally substituted aryl, alkyl,

8. All other definitions (of components Ar, R1-R3, W,Q) than stated above are withdrawn from further consideration by the examiner. Additionally, Claims 14, 15, 22, 24,26-33 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

First action on merits follows.

Information Disclosure Statement

9. The information Disclosure Statements provided as paper #2 dated 12/20/01; # 6 dated 6/3/02; # 7 dated 11/21/02; # 8 dated 4/23/03 are considered by examiner, and signed copies of PTO Form 1449 are enclosed with this communication for applicants' record.

Claim Objections

10. Claims 16-19 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 21. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is

proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 1-11,13,20,21,are rejected under 35 U.S.C. 102(a) as being anticipated by Chorvat et al (J. Med. Chem.42/5,833-848(March 1999), also cited as Chemical Abstract DN 130:209672)).

13. The ref. Compounds are encompassed by instant claims by Formula (I) wherein the variables are as:

W, Q = both of them N;
Ar = optionally substituted phenyl;
R1 = -N(C1-8Alkyl)2, -NH2,H, halogen, alkyl;
R2 = H, Halogen, alkyl;
R3 = - N-Mehtyl-2-pyridone, Optionally substituted aryl, alkyl.

Compounds having CAS RN # 220953-13-9 (= 9H-Purin-6-amine, N-butyl-9-(2-chloro-4,6,dimethoxyphenyl)-N-ethyl-2-methyl-8-phenyl), and CAS RN # 220952-86-4(=9H-Purin-4,6-dimethoxyphenyl-2-methyl-8-phenyl) are reading on to the ref. Chorvat.

14. Claims 1-11,13,20,21,are rejected under 35 U.S.C. 102(b) as being anticipated by Tangi et al(Heterocycles, 30/1,435-40(1990), also cited as Chemical Abstract DN 113:114920),

15. The ref. Compounds are encompassed by instant claims by Formula (I) wherein the variables are as listed in **13.** above.

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Compound having CAS RN # 129006-33-3(= 9H-Purine,2-chloro-8,9-dipheny) reads on to instant claims.

16. Claims 1-11,13,20,21,are rejected under 35 U.S.C. 102(a) as being anticipated by Young et al(J. Med. Chem.33/8,2073-80(1990), also cited as Chemical Abstract DN 113:58784).

17. The ref. Compounds are encompassed by instant claims by Formula (I) wherein the variables are as listed in **13.** above.

Compound having CAS RN # 127820-25-1(=

18. Claims 1-11,13,20,21,are rejected under 35 U.S.C. 102(a) as being anticipated by McKenzie et al(J. Heterocyclic Chem. 24,1551-53(1987).

19. The ref. Compounds are encompassed by instant claims by Formula (I) wherein the variables are as listed in **13.** above.

Compound No. 4 as recited on page 1551 in column 2 reads on to instant claims.

20. Claims 1-11,13,20,21,are rejected under 35 U.S.C. 102(a) as being anticipated by Nico et al(J. Org. Chem. 48/6,850-855(1983)).

21. The ref. Compounds are encompassed by instant claims by Formula (I) wherein the variables are as listed in **13.** above.

The compound listed in column 2 in page 854 (= 8-Phenyl-9-methylpurine) reads onto instant claims.

22. Claims 1-11,13,20,21,are rejected under 35 U.S.C. 102(a) as being anticipated by Bergmann et al(Tetrahedron,30, 3045-51(1974)).

23. The ref. Compounds are encompassed by instant claims by Formula (I) wherein the variables are as listed in **13.** above.

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Compound # 5 as listed in page 3046 reads onto instant claims.

Claim Rejections - 35 USC § 112

24. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

25. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply:

(A). Claims 1-13 recite "a condensed imidazole compound". The condensation is open ended and it included many compounds other than claimed herein. Correction to : " a compound of Formula (I), its pharmacologically acceptable salt or hydrates thereof" is required.

(B). Claim 20 recites: "comprising". Correction to "consisting of" is required.

Claim Rejections - 35 USC § 112

27. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 35 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating diabetes mellitus, does not reasonably provide enablement for preventing of diabetic complications, diabetic retinopathy, diseases against which the compound of claim 1 are effective. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

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nearly connected, to practice the invention commensurate in scope with these claims.

The claim includes the diseases yet to be discovered.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: (1). The nature of invention; (2). the state of prior art ; (3). the predictability or lack thereof in the art; (4). the amount of direction or guidance present; (5). the presence or absence of working examples; (6). the breadth of the claims, and (7). the quantity of experimentation needed.

Following references are cited to show the state of art:

▪ **Effect of other drug on adenosine receptors:**

Chou et al(PubMed Abstract 12602592, also cited as Am.J.Vet.Res. 64/2,216-24(Feb.2003)) state that: " Results of our study affirm the presence of guanine nucleotides binding protein linked adenosine receptors(i.e. high affinity A1 and A23a adenosine receptors) in equine forebrain tissues and reveal the antagonistic actions by caffeine and several biologically active caffeine metabolites".

Antagonism of adenosine actions in the equine CNS by instant compounds has not been disproved.

▪ **Earlier studies/investigations using "pentoxifyline" for diabetic vasculopathy:**

Antignani et al(PubMed Abstract 3602022, also cited as Pharmatherapeutica, 5/1, 50-6(1987)) state that: "changes in the biological indices after treatment were decreases in hamatocri. Mean corpuscular volume and blood fibrinogen values, but these were not statistically significant. The other variables showed little if any change."

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Specification on pages 58-62 recite tests and assays carried out for the instant compounds. Table 1 on page 62 recites test result for a single compound, namely Example 5 which is HCL salt. There is not comparison with the instant species of Example 46 which is a di-hydrate, and as well as art recognized reference.

The specification remains silent to point out any effect on the CNS system and blood pressure as investigated in the references stated earlier.

These results are not sufficient to support the methods of use claims not claiming treating of a specific cancer but in addition to treating, prevention of various cancers, and other diseases. Therefore, these results will help as preliminary guideline for screening the compounds only, and for preventing all the diseases as recited in the claims.

Statements of utility, which relate to or imply to treatment of a disease are subject to closer scrutiny. Ex parte Moore et al.(POBA 1960) 128 USPQ 8. Claim does not meet the Utility Guidelines. The claims do not qualify as one utility statement, and are not believable on their face. Claims will require too much experimentation to determine what patient dosage relationship would produce what results. It is not believable on its face that any one compound would have all of those utilities. In re Hozumi, 226 USPQ 353.

The instant claims relate not only to treatment of a specific disease, but also to prevention of other diseases as recited herein.

The quantity of experimentation need would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

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Thus, factors such as "sufficient working examples", "the level of skilled in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims involving use of compounds, and their compositions.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Claim Rejections - 35 USC § 101

28. Claim 36 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a process and step asserted utility or a well established utility.

The steps required for producing a preventive or therapeutic agent for diabetes mellitus, diabetiuc complications, diabetic retinopathy, or diseases against which the compound of claim 1 or an adenosine A2 receptor antagonist is used.

Claim 36 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a process or steps asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion


29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is 703 308 4709. The examiner can normally be reached on 6:30 to 5:00 pm (Monday-Thursday).

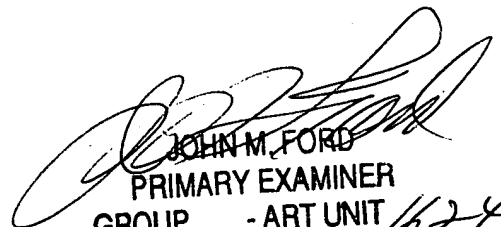
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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on 703 308 4716 or Sr. Examiner Mr. Richard Raymond at (703) 308 4523.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.


SP/June 20, 2003.


JOHN M. FORD
PRIMARY EXAMINER
GROUP - ART UNIT 1624